Claims

1. A crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide characterized by the following X-ray diffraction pattern obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta) = 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4, 14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0, 21.4, 22.7, 23.1 and 23.6 or a pharmaceutically acceptable salt thereof.

2. A crystalline modification of claim 1 further characterized by an infrared spectrum having sharp bands at 2925, 2854, 1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782, 705, 684 cm^{-1}.

3. A crystalline modification of claim 1 wherein the extrapolated melting point (DSC) is 137.2 °C.

4. A crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide characterized by the following X-ray diffraction pattern obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta) = 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4, 14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0, 21.4, 22.7, 23.1 and 23.6 and an infrared spectrum having sharp bands at 2925, 2854, 1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782, 705, 684 cm^{-1}, and wherein the extrapolated melting point (DSC) is 137.2 °C or a pharmaceutically acceptable salt thereof.

5. A crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide characterized by an infrared spectrum having sharp bands at 2925, 2854,

1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782, 705, 684 cm^{-1} or a pharmaceutically acceptable salt thereof.

6. A crystalline modification of claim 5 wherein the extrapolated melting point (DSC) is 137.2 °C.

7. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1 and a pharmaceutically acceptable carrier.

8. A pharmaceutically acceptable composition according to claim 7, wherein the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide is administered as powder in gelatine capsules.

9. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 2 and a pharmaceutically acceptable carrier.

10. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 3 and a pharmaceutically acceptable carrier.

11. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4 and a pharmaceutically acceptable carrier.

12. A pharmaceutically acceptable composition according to claim 11, wherein the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide is administered as powder in gelatine capsules.

13. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 5 and a pharmaceutically acceptable carrier.

14. A pharmaceutically acceptable composition according to claim 13, wherein the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide is administered as powder in gelatine capsules.

15. A pharmaceutically acceptable composition comprising the crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 6 and a pharmaceutically acceptable carrier.

16. A method of treating central nervous system disorders comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

17. A method of treating depression comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-

[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

18. A method of treating a disease selected from the group consisting of migraine, rheumatoid arthritis, asthma, bronchial hyperreactivity, allergic rhinitis, ocular inflammatory diseases, and oedema comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

19. A method of treating a disease selected from the group consisting of inflammatory bowel disease, Crohn's disease, induced vomiting, and emesis comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

20. A method of treating a disease selected from the group consisting of Parkinson's disease, anxiety, depression, Alzheimer's disease, psychoimmunologic or psychosomatic disorders, and psychosis comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

21. A method of treating a disease selected from the group consisting of multiple sclerosis, pain, headache, ocular injury, motion sickness, urinary incontinence, cancer, withdrawal symptoms of addictive drugs from opiates or nicotine, traumatic brain injury, and benign prostatic hyperplasia comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 1.

22. A method of treating central nervous system disorders comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

23. A method of treating depression comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

24. A method of treating a disease selected from the group consisting of migraine, rheumatoid arthritis, asthma, bronchial hyperreactivity, allergic rhinitis, ocular inflammatory diseases, and oedema comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

25. A method of treating a disease selected from the group consisting of inflammatory bowel disease, Crohn's disease, induced vomiting, and emesis comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

26. A method of treating a disease selected from the group consisting of Parkinson's disease, anxiety, depression, Alzheimer's disease, psychoimmunologic or psychosomatic disorders, and psychosis comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

27. A method of treating a disease selected from the group consisting of multiple sclerosis, pain, headache, ocular injury, motion sickness, urinary incontinence, cancer, withdrawal symptoms of addictive drugs from opiates or nicotine, traumatic brain injury, and benign prostatic hyperplasia comprising administering to an individual an effective amount of a crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide according to claim 4.

28. A process for the manufacture of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide as defined in claim 1 comprising

(a) dissolving 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in 2-propanol under reflux conditions;

(b) subjecting the solution in (a) to polishing filtration;

(c) cooling the solution while stirring over a period of about 6 hours to a temperature of about 10°C;

(d) stirring the slurry at about 10°C until crystals form; and

(e) harvesting the crystals by filtration.

29. A process for the manufacture of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide as defined in claim 1 comprising

(a) dissolving 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in 1-propanol under reflux conditions;

(b) subjecting the solution in (a) to polishing filtration;

(c) cooling the solution while stirring over a period of about 6 hours to a temperature of about 10°C;

(d) stirring the slurry at about 10°C until crystals form; and
(e) harvesting the crystals by filtration.

30. The process of claim 28 wherein the 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide employed in step (a) is prepared by the process comprising
(a) reacting magnesium, 2-bromo-5-fluorotoluene, and N-tert-butyl-6-chloronicotinamide under reflux to produce N-tert-butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide;
(b) isolating the N-tert-butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide;
(c) reacting N-tert-butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide with potassium carbonate and thiomorpholine to produce N-tert-butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide;
(d) isolating the N-tert-butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide;
(e) adding methanesulfonic acid dropwise to the N-tert-butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide to produce an emulsion to produce 4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide;
(f) isolating the 4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide;
(g) reacting 4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide and potassium hydroxide, methanol, and (diacetoxyiodo)benzene to produce [4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-carbamic methyl ester;
(h) adding a solution of Red-Al dropwise to the [4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-carbamic methyl ester to produce methyl-[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-amine;
(i) adding a solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride dropwise into a solution of the methyl-[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-amine to produce 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-isobutyramide; and
(j) treating the 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-isobutyramide with potassium

peroxymonosulfate at room temperature followed by cooling to about 0°C followed by the dropwise addition of sodium hydrogen sulfite solution to produce 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide.